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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte FRANK A. SKRALY and MARTHA SHOLL

Appeal 2008-004223[1]
Application 09/909,574
Technology Center 1600

Decided: [2]July 10, 2009

Before TONI R. SCHEINER, RICHARD M. LEBOVITZ, and STEPHEN WALSH, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] Heard May 14, 2009.

[2] The two-month time period for filing an appeal or commencing a civil action, as provided for in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This is a decision on the appeal from the Patent Examiner's obviousness rejection of claims 1-4 and 6-10. Jurisdiction for this appeal is under 35 U.S.C. § 6(b). We affirm the rejection.

STATEMENT OF THE CASE

The claimed invention is to processes for producing polyhydroxyalkanoates (PHAs) from genetically engineered bacteria, plants, and yeast. PHAs are biodegradable thermoplastic polyesters which are "replacements for petrochemical polymers currently in use for packaging and coating applications" (Madison, 63 MICRO. MOL. BIO. REVS. 21, 24 1999).

The Patent Examiner rejected claims 1-4 and 6-10 under 35 U.S.C. § 103(a) as obvious over Skraly (*Polyhydroxyalkanoates Produced by Recombinant E. coli*, Poster at Engineering Foundation Conference: Metabolic Engineering, 1998), Madison, and the BRENDA database (Entry for "EC 1.1.1.202") (Ans. 3). Appellants appeal the rejection. Claim 1, which is representative of the appealed subject matter, reads as follows:

> 1. A method for producing polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast, which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organisms are genetically engineered to express enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, which can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydrxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are

polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

STATEMENT OF THE ISSUES

The Examiner found the process recited in claim 1 obvious in view of the teachings in the Skraly, Madison, and BRENDA publications. Appellants contend that the Examiner's rejection was improper. The main issues in the rejection as raised by Appellants are as follows:

Claim 1

Did the Examiner err in finding that Skraly suggested converting a diol substrate to one of the specifically claimed hydroxyalkanoate monomers in a process of producing PHAs?

Did the Examiner err in finding the claimed process comprising the use of organisms genetically engineered to express enzymes "selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase" obvious over Skraly's process of culturing genetically engineered *E. coli* expressing diol oxidoreductase and glycerol dehydratase in the presence of substrate and coenzyme B-12?

Did the Examiner err in finding the claimed method for producing recombinant PHA having a mass of at least 300,000 Da obvious in view of Madison's teaching of producing PHA in a range of 50,000 to 1,000,000 Da?

Claim 8

Did the Examiner err in finding it obvious to genetically engineer an organism to express a diol reductase and aldehyde dehydrogenase in view of Skraly, Madison, and BRENDA?

PRINCIPLES OF LAW

"[T]he ultimate determination of obviousness 'does not require absolute predictability of success. ... [A]ll that is required is a reasonable expectation of success.' *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988); *see also In re Longi*, 759 F.2d 887, 897(Fed. Cir. 1985)." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000).

When there is a range disclosed in the prior art, and the claimed invention overlaps or falls within that range, there is a presumption of obviousness. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003*); Iron Grip Barbell Co. v. USA Sports*, 392 F.3d 1317, 1322 (Fed. Cir. 2004).

> The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. These cases have consistently held that in such a situation, the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.

In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990). (Internal citations omitted.)

It is well-established that in such cases obviousness can be rebutted by secondary considerations, such as a showing of "new and unexpected results relative to the prior art." *Iron Grip Barbell Co*., 392 F.3d at 1322. The showing must be factual; argument or conclusory statements do not suffice. *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997).

FACTS[3]

Skraly

1. Skraly describes genetically engineered recombinant systems to produce novel PHA compositions using new synthetic pathways (Skraly, at 2).

2. "Recombinant systems . . . can be used to generate entirely novel PHA compositions with a wide range of material properties because any combination of PHA genes may be used, and the composition is determined only by what genes are added" (*id.*).

3. The system "allows manipulation of the polymer structure/function design space available with over 100 different monomer types" (*id.*).

4. Skraly teaches engineering new PHA polymers starting with monomer precursors which are converted to "hydroxy acids", also known as hydroxyalkanoates (Skraly, at 4).

5. Skraly describes several novel example PHA compositions produced by a recombinant *E. coli* genetically engineered with a recombinant PHA synthase gene (Skraly, at 7).

6. The substrates utilized in the examples included: 1) 4-hydroxybutyrate and 1,4-butanediol; 2) 1,3-propanediol; and 3) 1,5-pentanediol (Skraly, at 7).

7. Additionally, Skraly describes a recombinant *E. coli* expressing aldehyde dehydrogenase and CoA transferase, and genetically engineered with recombinant glycerol dehydratase and 1,3-propanediol reductase genes, which enabled the recombinant to produce PHB-co-HV (a block copolymer) from 1,2-propanediol (Skraly, at 9-10).

8. The glycerol dehydratase enzyme requires coenzyme B-12 for activity (Skraly, at 10). Skraly states that the addition of the B-12 controls the

[3] Findings and conclusions of fact ("F").

composition of the 3HV- and 3HP-containing copolymers from the 1,2-propanediol substrate (Skraly, at 9-10).

Madison

9. Madison describes several different approaches to produce PHA using genetically engineered bacteria, providing evidence that persons of ordinary skill in the art were capable of constructing recombinant organisms with different genes to facilitate the production of PHA (Madison, at 41-44; Ans. 4).

10. Madison teaches producing PHA microorganisms and that the molecular mass of PHA per PHA producer varies from 50,000 to 1,000,000 Da (Madison, at 22, col. 2).

BRENDA

11. BRENDA discloses various diol reductases from bacteria and other organisms (Ans. 5).

Claim 1

12. Claim 1 is drawn to a method of producing PHA comprising:

13. "providing" a bacteria, plant, or yeast organism which expresses "enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase";

14. the organisms are genetically engineered to express "enzymes . . . selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase";

15. the genetically engineered enzymes "can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate"; and

16. "culturing the organisms" to polymerize the hydroxyalkanoate monomers by the PHA synthase enzyme to form PHA.

17. The PHA has a weight-average molecular weight of at least 300,000 Da.

18. Claim 3 is to the process of claim 1, where "the diol is 1,5-pentanediol and the hydroxyalkanoate monomer is 5-hydroxyvalerate."

19. Claim 4 is to the process of claim 1, where "the diol is 1,4-butanediol and the hydroxyalkanoate monomer is 4-hydroxybutyrate."

20. Claim 7 is to the process of claim 7, where "the diol is 1,2-propanediol and the hydroxyalkanoate monomer is 2-hydroxypropionate."

The limitations of claim 1 are met by Skraly as follows:

21. "Providing" step (F13): providing bacteria with PHA synthase enzymes (F5) and CoA transferase (F7);

22. "Genetically engineered" step (F14): genetically engineering the bacteria to express a diol oxidoreductase ("1,3-propanediol reductase" (F7));

23. "Culturing" step (F15-16): growing ("culturing") the cells in the presence of diol substrates to produce PHAs (F2-4, 6, & 7).

ANALYSIS

Claims 1 and 8

As established by the Skraly and Madison publications, it was known prior to the filing date of the instant application that PHAs could be

produced by genetically engineered bacteria. The instant application describes the production of PHAs by *E. coli* that had been genetically engineered to express aldehyde dehydrogenase ("*aldH*"; Spec. 9:29-30) and 1,3 propanediol oxidoreductase ("*dhaT*"; Spec. 11:27) using a diol (such as "1,4-BD") as a substrate (Spec. 16:8-20; *E. coli* are transformed with "pMS59", which contains the aldehyde dehydrogenase and 1,3 propanediol oxidoreductase genes).

Claim 1 in this Appeal is directed to a process in which organisms[4] expressing one of several specifically recited enzymes involved in PHA synthesis are provided and genetically engineered to express a diol oxidoreductase or an aldehyde dehydrogenase (F13-14). The enzymes introduced into the organisms by genetic engineering are required by the claim to be capable of converting a diol into one of several specifically recited hydroxyalkanoate monomers, which are polymerized in subsequent steps to form PHA (F15). The organism is then cultured to produce the PHA (F16), presumably using the diol as a substrate to form the hydroxyalkanoate monomer, but this synthetic step is not expressly recited in the claim.

The Examiner found that Skraly taught a process of providing *E. coli* expressing PHA synthetic enzymes which had been engineered with a diol reductase as required by claim 1 (Ans. 3; F7). The Examiner also found that Skraly taught using a diol as substrate for PHA production as recited in claim 1 (*id.*). The Examiner acknowledged that Skraly did not teach the hydroxyalkanoate monomers recited in claim 1, but concluded that persons of ordinary skill in the art would have had reason to use suitable diol precursors to produce the claimed monomers, motivated by Skraly's

[4] The organisms can be bacteria, plants, or yeast.

teaching of the desirability of producing PHA from non-natural recombinant pathways (*see* Ans. 10).

Diols into hydroxyalkanoate monomers

Appellants contend that Skraly does not disclose a system which can convert diols into hydroxyalkanoate monomers "selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate" as recited in claim 1 (App. Br. 10).

Appellants' argument is not supported by the evidence. On page 9, Skraly describes *E. coli* genetically engineered to express a diol reductase – the same as in claim 1 (F7, 22). The *E. coli* used 1,2-propanediol as a substrate (F7) – the same diol recited in claim 7 – to produce PHA. Skraly describes converting a monomer diol precursor to a hydroxyacid – a "hydroxyalkanoate monomer" (F4) as in claim 1 – which in turn is polymerized into PHAs. Thus, Skraly teaches converting diols into hydroxyalkanoate monomers.

The scheme shown on page 9 of Skraly does not show any of the hydroxyalkanoate monomers recited in claim 1. However, the Examiner found that persons of ordinary skill in the art would have considered it obvious to have chosen a diol substrate capable of being converted into at least one of the recited hydroxyalkanoate monomers based on the combined teachings of Skraly, Madison, and BRENDA.

The Examiner's position is supported by the evidence. Skraly states that recombinant systems can be devised with "any combination of PHA

genes" to allow "manipulation of the polymer structure/function design space available with over 100 different monomer types" (F1-3). In other words, Skraly expressly suggests choosing different genes and monomer types to produce desired PHA compositions. Given the explicit suggestion to do so, persons of ordinary skill in the art would have reasonably expected that different substrates and genes could be used successfully to make PHAs.

Furthermore, Skraly describes examples in which genetically engineered bacteria were used to convert the diols 1,5-pentanediol and 1,4-butanediol (F6) into PHA, the same substrates recited in claim 3 and 4, respectively. Based on the presence of diol oxidoreductase and aldehyde dehydrogenase in *E. coli* (F7) – the same enzymes utilized in claim 1 – it would have been reasonable to believe that utilizing 1,5-pentanediol or 1,4-butanediol in the experiment described on page 9 of Skraly would result in conversion to at least one of the hydroxyalkanoate monomers listed in claim 1. Appellants have not provided evidence to the contrary.

Appellants also contend there is "no basis to conclude that one would genetically engineer the organisms as appellants have done, make the substitutions in feedstock that appellants have done, to produce the claimed polymers, based on this disclosure" (App. Br. 11).

To the contrary, as discussed already, PHA production using genetically engineered organisms was known in the prior art before the instant application was filed. Skraly describes several different approaches to recombinant PHA production (Ans. 9), as does Madison (F9). Skraly expressly suggests using different genes and substrates to produce novel and new PHAs (F1-3), providing an express reason to engineer bacteria as Appellants have done. In fact, the only apparent difference between the

claimed process and that of Skraly is that Skraly does not expressly state that its enzymes are capable of converting diols into the specifically recited hydroxyalkanoate monomers. However, Skraly teaches using diols as starting substrates and describes their conversion into hydroxyalkanoates (F4).

Appellants assert that one "cannot simply string together several genes together like toy blocks and expect a complex metabolic pathway to work in a living organism" (App. Br. 13). This argument is not persuasive. Skraly expressly states that "any of combination of PHA genes may be used" to generate PHA compositions (F2). Thus, contrary to Appellants' argument, the prior art did not doubt that PHA genes could be linked together to form PHA compositions with a reasonable expectation of success. Moreover, claim 1 does not require several genes to be strung together. Instead, it requires that only one be engineered – a diol oxidoreductase or an aldehyde dehydrogenase.

Glycerol dehydratase, B-12, and thiolase

Appellants contend that "the claimed method does not employ glycerol dehydratase, or the mandatory coenzyme B-12 that would be needed for organisms such as *E. coli* which cannot synthesize coenzyme B-12, or a second thiolase to convert propionyl CoA (from 1,2-propanedial) to 3-hydroxyvaleryl-CoA" as does the process described by Skraly (App. Br. 2-3).

This argument does not persuade us that the Examiner erred. Claim 1 does not exclude dehydratase, coenzyme B-12, or a thiolase from being used in the claimed process. Therefore, while it may be correct that these

materials were omitted from the process described in the Specification (*see* Spec. 16:8-20), Appellants have not written a claim that excludes them from the process which is claimed.

Molecular weight limitation

Claim 1 recites that the recombinant PHA has a molecular weight of "at least 300,000 Da." The Examiner finds that such a molecular weight would have been reasonably expected in view of Madison's teaching that PHA producers make PHAs with molecular weights in the range of from 50,000 to 1,000,000 Da (F10). Appellants contend:

> This is not tantamount to a disclosure that the molecular mass of all polyhydroxyalkanoates is invariably in the order of 50,000 to 1,000,000 Da in every polyhydroxyalkanoate producer, let alone in genetically engineered organisms producing PHA with the monomer content recited in claim 1. Furthermore, Madison also discloses conditions in which the molecular mass of poly-3-hydroxyalkanoate obtained was less than 50,000. Even if disclosure in Madison were limited to the mass range cited by the Examiner, knowledge of the mass range of poly-3-hydroxyalkanoates does not make obvious every and any genetically engineered pathway that produces PHAs in that size range.

(Reply Br. 4-5.)

It is well-established when there is a range in the prior art, and the claimed invention overlaps or falls within it, there is a presumption of obviousness. Here, the claimed range "of at least 300,000 Da" overlaps with the prior art range of from 50,000 to 1,000,000 Da. Accordingly, the Examiner correctly presumed the claimed range to be obvious. The presumption can be rebutted by secondary considerations, such as showing that the claimed range is critical. Such a showing must be "relative to the

prior art." *Iron Grip Barbell Co.*, 392 F.3d at 1322. However, in this case, Appellants have not provided evidence that the recited range of "at least 300,000 Da" is critical as compared to the prior art range.

With regard to the argument that Madison shows PHAs produced of less than 50,000 Da, we note that Madison in fact explains how substrate concentrations influence molecular weight and teaches how to achieve masses of over 1,000,000 Da (Madison, at 39, column 2). Thus, Madison establishes that persons of skill in the art would have recognized that culture conditions affect molecular mass and would have known to vary such result effective parameters to achieve a molecular weight of the desired size.

Aldehyde dehydrogenase and diol reductase

Appellants contend that Skraly does not disclose genetically engineering an aldehyde dehydrogenase in *E. coli* (App. Br. 6).

Claim 1 does not require that the organism be engineered to express the aldehyde dehydrogenase. The claim recites that enzymes are "selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase." We therefore interpret the claim to require the organism be genetically engineered with either the diol oxidoreductase or aldehyde dehydrogenase, but not necessarily both. Skraly describes an *E. coli* engineered to express a diol oxidoreductase (F7), and therefore meets the claim limitation.

With respect to claim 8 which requires both the diol oxidoreductase and aldehyde dehydrogenase (App. Br. 15), Skraly discloses that alcohol dehydrogenase is a part of the PHA pathway (F7). The Examiner provided evidence that alcohol dehydrogenase had been cloned, expressed in *E. coli*,

and was capable of acting on diol substrates (Ans. 14). Therefore, the Examiner's conclusion that it would have been obvious to utilize the cloned gene in *E. coli* to enhance PHA production is factually supported. Appellants have not identified a defect in the Examiner's fact-finding or reasoning.[5]

Claims 2-4, 6, and 7

Claims 2-4, 6, and 7 specify specific diols and hydroxyalkanoate monomers for use in the process of claim 1. Based on Skraly's teachings that any combination of genes could be used with over 100 different monomer types (F3) to produce PHA compositions and that different diol substrates could be utilized by *E. coli* to manufacture PHA (F4, 6, 7), it is reasonable to conclude that persons of ordinary skill in the art could have routinely selected any desired diol substrate for Skraly's process, including those recited in the claims. The Examiner found that persons of skill in the art would have been prompted to choose a diol as a "cheap substrate" for producing PHA compositions (Ans. 11), and thus has identified a reason for finding the claimed subject matter obvious. Appellants have not identified a flaw in this reasoning.

Claims 9

Claim 9 is drawn to the method of claim 8 where the organism "is selected from the group consisting of *Escherichia coli, Ralstonia eutropha,*

[5] At the hearing, Appellants raised a new argument that MW of 300 kD cannot be achieved without genetically engineered ADH. Appellants did not provide evidence to support that theory. As claim 1 does not require genetically engineered ADH, we give the argument no weight as applied to that claim. As Appellants provide no evidence or comparative data to support the theory, we are not persuaded that the rejection of claim 8 should be reversed.

Klebsiella spp., *Alcaligenes latus, Azotobacter* spp., and *Comamonas* spp." Skraly teaches *E. coli* and therefore meets the limitations of the claim.

Claim 10

Appellants make the same argument as they did for claim 1. As these arguments were not persuasive for claim 1, they are also not persuasive for claim 10 which involves the same process steps.

CONCLUSIONS OF LAW

The Examiner did not err in concluding:

• that Skraly suggested converting a diol substrate to one of the specifically recited hydroxyalkanoate monomers in a process of producing PHAs;

• the claimed process comprising the use of organisms genetically engineered to express enzymes "selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase" was obvious over Skraly's process of culturing genetically engineered *E. coli* expressing diol oxidoreductase and glycerol dehydratase in the presence of substrate and coenzyme B-12;

• the claimed method for producing recombinant PHA having a mass of at least 300,000 Da was obvious in view of Madison's teaching that PHA producers make PHA with a molecular mass in the range of 50,000 to 1,000,000 Da; and

• it was obvious to genetically engineer an organism to express a diol reductase and aldehyde dehydrogenase in view of Skraly, Madison, and BRENDA.

SUMMARY

The obviousness rejection of claims 1-4 and 6-10 is affirmed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

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